



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB99/01170 <b>(22) International Filing Date:</b> 16 April 1999 (16.04.99)  <b>(30) Priority Data:</b> 9808189.6 17 April 1998 (17.04.98) GB  <b>(71) Applicants (for all designated States except US):</b> UNIVERSITY COLLEGE LONDON [GB/GB]; Rowland Hill Street, London NW3 2PF (GB). UNISEARCH LIMITED [AU/AU]; Unisearch House, 221-227 Anzac Parade, Kensington, NSW (AU).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> REVELL, Peter, Allen [GB/GB]; 17 Willowdene Court, Warley, Brentwood, Essex CM14 5ET (GB). HOWLETT, Cameron, Rolfe [GB/AU]; 49 McIntosh Street, Gordon, NSW 2072 (AU).  <b>(74) Agents:</b> DANIELS, Jeffrey, Nicholas et al.; Page White & Farrer, 54 Doughty Street, London WC1N 2LS (GB).		<b>(81) Designated States:</b> AU, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> BONE IMPLANT  <b>(57) Abstract</b>  A bone implant having a surface comprising a bioactive material, said bioactive material having incorporated therein ions from one or more of the groups of the periodic table consisting of groups IIA, IVA, VIIA and transition elements, said bioactive material being a material that is capable of promoting bone growth onto the bone implant.		

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## BONE IMPLANT

### FIELD OF THE INVENTION

The present invention relates to a bone implant having improved bone ongrowth properties, and a method for treating a bone implant to improve these properties.

### BACKGROUND TO THE INVENTION

A major problem in orthopaedic reconstruction surgery, and in particular in joint replacement surgery, relates to the need to anchor permanently an orthopaedic implant to the skeleton. Usually, whilst bone grows up to the orthopaedic implant, it does not become physically and chemically bonded to the implant.

There are several known methods for achieving anchoring of orthopaedic implants to the skeleton. According to one commonly-known method, a "cement" is used to increase the surface area of the implant thereby to increase its interlock with the bone. Acrylic cements are commonly used for this purpose. However, over extended periods of time, problems are encountered with deterioration of the cement and the consequent loosening of the bone implant from the skeleton.

Another known method for attempting to anchor orthopaedic implants to the skeleton involves designing the implant to have a beaded or porous surface so that bone growing towards the implant will provide an interference fitting between the implant and the ingrowing skeletal tissues (e.g. bone).

A third method for achieving anchoring of an orthopaedic implant into the skeleton involves the use of an implant that includes a coating of a bioactive material such as hydroxyapatite. Bioactive materials are materials that are capable of promoting bone growth onto the implant, and include materials such as fluoroapatite, tricalcium phosphate, glass ionomers and bioactive glass such as Bioglass and AW Glass Ceramic, in addition to hydroxyapatite (HA). Orthopaedic implants having HA coatings

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currently provide more effective fusion of the implant with the skeleton than other known anchoring techniques.

Since the long term success of orthopaedic implants is highly dependent on the anchoring of the orthopaedic implant to the skeleton, many investigations have been made into other techniques for improving anchoring.

Previously published studies<sup>1,2,3</sup> have investigated whether modifying the surface chemistry of uncoated structures (some of which are suitable for use as orthopaedic implants) by the incorporation of cations such as magnesium ( $Mg^{++}$ ) enhances the adhesion of human bone-derived cells to these uncoated structures in *in vitro* studies. Incorporation of cations into ceramic or metallic structures in these previous studies was accomplished by ion beam implantation (embedding), which enables the incorporation of the cations into the ceramic or metallic surface atomic layers without affecting the surface properties thereof. The studies resulted in mixed success.

Accordingly, there still exists a need to develop bone implants having improved bone ongrowth properties, and methods for manufacturing such bone implants.

#### SUMMARY OF THE INVENTION

According to the present invention there is provided a bone implant having a surface comprising a bioactive material, said bioactive material having incorporated therein ions from one or more of the groups of the period table consisting of groups IIA, IVA, VIIA and transition elements, said bioactive material being a material that is capable of promoting bone growth into and/or onto the bone implant, and said ions being capable of improving the bone ongrowth properties.

Preferably the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIII, IB, IIB, IVA and VIIA.

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Preferably, the bioactive material comprises hydroxyapatite, and preferably the ions are incorporated into the surface of the bone implant by ion beam implantation or cathodic arc deposition.

The inventors have conducted an *in vivo* study in order to investigate whether the incorporation of ions by ion beam implantation techniques into bioactive material coated metal/metal alloy and/or orthopaedic implants (specifically hydroxyapatite) enhances bone growth onto the orthopaedic implant. The inventors have surprisingly discovered that the addition of particular ions to these coatings greatly enhances bone ongrowth onto the implant when compared with conventional hydroxyapatite (HA) coated metal alloy orthopaedic implants.

The growth of human bone cells onto a surface depends critically on the nature of the surface. Accordingly, whilst it is possible to use methods other than ion beam implantation (embedding) of the ions into the surface of the bone implant (e.g. cathodic arc deposition or formulating the surface of the bone implant to include such ions during formation of the bone implant), ion beam embedding is preferred since this method results in altering the surface chemistry of the surface material without affecting the surface structure and mechanical properties. Accordingly, if another method is used to provide a surface of a bone implant comprising a bioactive material having incorporated therein ions from one or more of the selected groups of the periodic table, care must be taken to ensure that the surface structure and mechanical properties of the surface are as close to the unmodified bioactive material surface properties as possible.

The ions should be present in the surface of the bone implant at a level sufficient to achieve enhanced bone ongrowth but not at so great a level as to affect the mechanical and surface properties of the surface.

Preferably, the ions are incorporated into the surface of the bone implant up to a maximum depth of 200nm. Whilst this is the preferred maximum depth of ions, it is possible to implant ions

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to greater depths, for example 1000nm. However, by implanting ions to these greater depths, there is an increasing risk that the surface and mechanical properties of the hydroxyapatite might be affected, due to the higher temperatures generated to achieve implantation of the ions to these depths. The higher temperatures are reached as a result of the greater energies used in ion beam implantation of the ions into the surface of the bioactive material.

Preferably, the ions are incorporated into the surface of the bone implant up to a maximum depth of 150nm, and preferably at depths ranging up to approximately 100nm.

Preferably, the ions are present in the surface of the bone implant at a level of between  $1 \times 10^{14}$  and  $1 \times 10^{18}$  ions per  $\text{cm}^2$  of the surface. These dosage levels correspond to ion beam implantation energies up to approximately 100 kV.

Preferably the ions incorporated into the surface of the bone implant comprise the ions of elements that can form divalent cations, with the exception of silicon. Examples of such ions include the cations of iron, including ferrous and ferric ions, since iron is capable of forming the divalent ferrous cation.

Preferably, the ions incorporated into the surface of the bone implant comprise cations that are involved in metabolic processes in trace amounts.

Preferably the ions incorporated into the surface of the bone implant comprise one or more of the following:

magnesium, calcium, strontium, titanium, chromium, manganese, iron, copper, zinc, silicon and fluorine ions.

Preferably, the ions incorporated into the surface of the bone implant are from one or more of the groups of the periodic table consisting of groups IIA, VIIB, IIB, IVA and VIIA.

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More preferably, the ions comprise magnesium, manganese, zinc or silicon ions.

In the case of a bone implant for use in total joint replacements, such as hip replacements, the bone implant will usually comprise a body portion coated with a hydroxyapatite coating. It is preferred that the body portion be formed of a metal or metal alloy, such as cobalt-chrome or titanium alloy.

In the case of dental implants, the body portion may comprise a pin formed of a metal alloy coated by a hydroxyapatite coating, which is inserted into the jaw to replace a tooth.

However, it is not always necessary to use a body portion in the bone implant. The present inventors have found that it is also possible to use a bioactive material such as hydroxyapatite without a structural body portion to promote healing in a bone. According to the present invention there is also provided a bone implant wherein the bone implant substantially comprises a bioactive material (preferably hydroxyapatite) and no body portion. In this case, the bone implant is preferably in a granular form. The granular bioactive material embedded with ions of the selected groups of the periodic table can be used in the mending of fractured or defective bones. The granular ion beam implanted hydroxyapatite bone implant material can be packed into the area of the break or defect in the bone. Since this material has excellent bone growth enhancing properties, this material can be advantageously used to speed up the process of bone repair.

According to the present invention there is also provided a method of treating a bone implant having a surface comprising a bioactive material to improve the bone ongrowth properties of the bone implant, comprising subjecting the bone implant to ion beam implantation to thereby incorporate ions from one or more of the groups of the periodic table consisting of groups IIA, IVA, VII A and transition elements into the surface thereof.

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Preferably the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIII, IB, IIB, IVA and VIIA.

Preferably, the bioactive material comprises hydroxyapatite.

Preferably, the ions are incorporated into the surface of the bone implant at a level of between  $1 \times 10^{14}$  and  $1 \times 10^{18}$  ions per  $\text{cm}^2$  of the surface.

#### BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 shows the percentage of bone ingrowth into an implant slot after 6 weeks of implantation in rabbit femur using an implant according to the invention as compared with a prior art implant.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention will now be described in further detail by reference to the following *in vivo* experimental implantation study.

Cylindrical titanium alloy implants (Ti6Al4V) (4.5 diam x 6mm length) with a slot (2 x 2 x 4 mm) in one side were plasma-spray HA-coated at the bottom of the slot (HA-Ti6Al4V). Identically prepared cylinders were additionally ion beam implanted with  $\text{Mg}^{++}$  on the HA-coated region using a metal vapour vacuum arc (MEVVA) ion source (Mg-HA-Ti6Al4V) ( $1 \times 10^{17}$  ions/ $\text{cm}^2\text{Mg}^{++}$ ). Surgical implantation was performed under general anaesthetic with full sterile precautions into the lateral side of the lower femur of female NZ white rabbits (n=6). A 4.5 mm diameter hole was made using a saline cooled diamond-impregnated trephine and the sterile cylinders (autoclave,  $121^\circ\text{C}$ , 15 mins) inserted bilaterally. HA-Ti6Al4V was implanted on the left, Mg-HA-Ti6Al4V on the right. Fluorescent bone labels (tetracycline, calcein blue, calcein green, alizarin red) were administered at weekly intervals and animals killed at 6 weeks. Retrieved femurs were



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processed in resin and ground sections ( $30\mu\text{m}$ ) prepared with the implant *in situ* (Exakt System, Hamburg, Germany). The maximum distance that each label had reached in the slots was measured by fluorescence microscopy using an eye-piece graticule and the result expressed as percentage bone ingrowth. The area occupied by new bone after 6 weeks was measured in toluidine blue stained sections using a Quantimet 500 (Leica, Cambridge, UK) and expressed as percentage area of bone formation.

### Results and Discussion

The percentage of bone ingrowth was significantly higher in Mg-HA-Ti6Al4V than in HA-Ti6Al4V implants at 3, 4 and 5 weeks ( $p < 0.05$ ) (Student's 't' test) (see Fig. 1). No significant differences were found at 1 and 2 weeks, though Mg-HA-Ti6Al4V mean values were higher. At 6 weeks, the percentage area of bone formation was significantly greater in the slots with Mg-HA-coating ( $25.73 \pm 9.12\%$ ,  $n=5$ ) compared with HA-coating alone ( $5.86 \pm 3.46\%$ ,  $n=5$ ) ( $p < 0.05$ , Student's 't' test).

These results demonstrate that  $\text{Mg}^{++}$  ion embedding of an HA-coating increases bone growth into a slot in a Ti6Al4V alloy implant when compared with conventional HA.

As will be appreciated by persons skilled in the art of the invention, whilst the experimental implantation study was conducted using magnesium ion embedding, other ions from the groups of the periodic table consisting of groups IIA, IVA, VIIA and transition elements will also result in enhanced bone formation when compared with conventional HA-coated implants.

It will also be appreciated by persons skilled in the art of the invention that ions deleterious to bone mineralisation, such as aluminium (which is implicated in various bone diseases), would not result in enhancement of bone formation. The studies of the present inventors confirm that aluminium and other ions deleterious to bone mineralisation cannot be used in the present invention to increase bone formation.

## References

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**CLAIMS:**

1. A bone implant having a surface comprising a bioactive material, said bioactive material having incorporated therein ions from one or more of the groups of the periodic table consisting of groups IIA, IVA, VIIA and transition elements, said bioactive material being a material that is capable of promoting bone growth onto the bone implant.
2. The bone implant as claimed in claim 1, wherein the bioactive material comprises hydroxyapatite.
3. The bone implant as claimed in claim 1 or claim 2, wherein the ions are incorporated into or onto the surface thereof by ion beam implantation or cathodic arc deposition.
4. The bone implant as claimed in claim 3, wherein the ions are incorporated into the surface atomic layers of the bone implant up to a maximum depth of 200nm.
5. The bone implant as claimed in claim 3, wherein the ions are incorporated into the surface of the bone implant up to a maximum depth of 150 nm.
6. The bone implant as claimed in claim 5, wherein the ions are incorporated into the surface at depths ranging up to approximately 100nm.
7. A bone implant as claimed in any one of the preceding claims wherein the ions are present at a level of between  $1 \times 10^{10}$  and  $1 \times 10^{18}$  ions per  $\text{cm}^2$  of the surface.
8. A bone implant as claimed in any one of the preceding claims, wherein the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIIB, VIII, IB, IIB, IVA and VIIA.

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9. A bone implant as claimed in claim 8, wherein the ions comprise one or more of the following:

magnesium, calcium, strontium, titanium, chromium, manganese, iron, copper, zinc, silicon and fluorine ions.

10. A bone implant as claimed in claim 8, wherein the ions incorporated into the surface of the bone implant are from one or more of the groups of the periodic table consisting of groups IIA, VIIB, IIB, IVA and VIIA.

11. A bone implant as claimed in any one of the preceding claims, wherein the ions comprise magnesium, manganese, zinc or silicon ions.

12. A bone implant as claimed in any one of the preceding claims, comprising a body portion coated with a bioactive material coating.

13. A bone implant as claimed in claim 12, wherein the body portion is formed of a metal or a metal alloy, preferably a titanium alloy.

14. A bone implant as claimed in any one of claims 1 to 11, wherein the bone implant substantially comprises a bioactive material.

15. A bone implant as claimed in claim 10, wherein the bone implant is in granular form.

16. A method of treating a bone implant having a surface comprising a bioactive material to improve the bone ongrowth properties of the bone implant comprising subjecting the bone implant to ion beam embedding thereby to incorporate ions from one or more of the groups of the periodic table consisting of groups IIA, IVA, VIIA and transition elements into the surface.

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17. The method as claimed in claim 16, wherein the bioactive material comprises hydroxyapatite.

18. The method as claimed in any one of claim 16 or claim 17, wherein the ions are incorporated into the surface up to a maximum depth of 200nm.

19. The method as claimed in claim 18, wherein the ions are incorporated into the surface up to a maximum depth of 150nm.

20. The method as claimed in claim 19, wherein the ions are incorporated at depths ranging up to approximately 100nm.

21. The method as claimed in any one of claims 15 to 20, wherein the ions are present at between  $1 \times 10^{10}$  and  $1 \times 10^{18}$  ions per  $\text{cm}^2$  of the implant surface.

22. The method as claimed in any one of claims 15 to 21, wherein the ions are selected from one or more groups of the periodic table consisting of groups IIA, IVB, VIB, VIIB, VIII, IB, IIB, IVA and VIIA.

23. The method as claimed in claim 22, wherein the ions comprise one or more of the following:

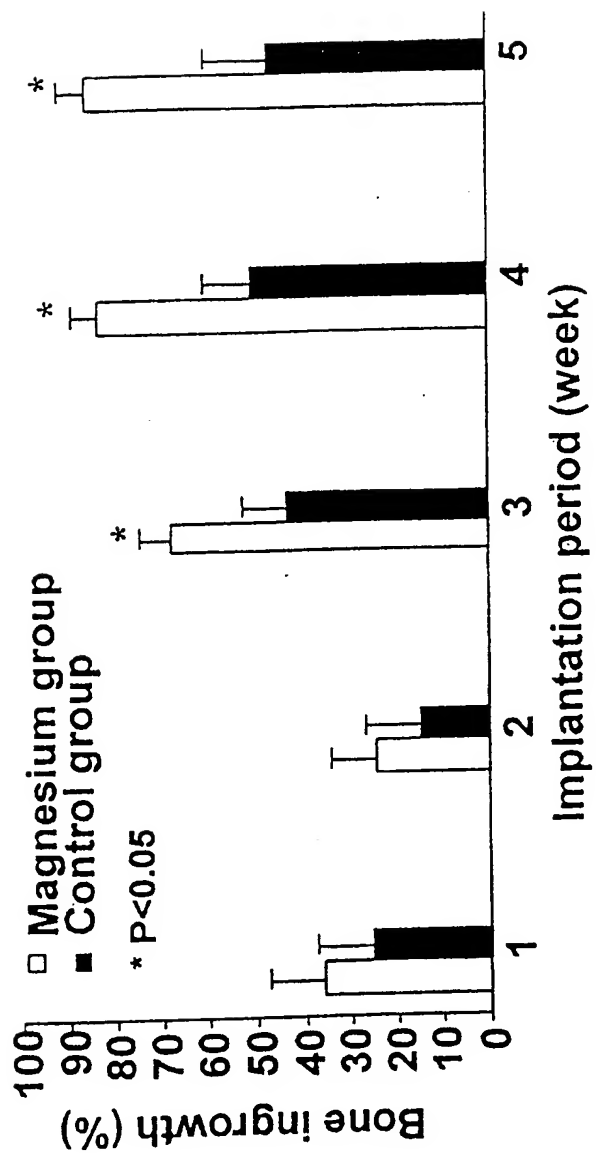
magnesium, calcium, strontium, titanium, chromium,  
manganese, iron, copper, zinc, silicon and fluorine ions.

24. The method as claimed in claim 22, wherein the ions incorporated into the surface of the bone implant are from one or more of the groups of the periodic table consisting of groups IIA, VIIB, IIB, IVA and VIIA.

25. The method as claimed in claim 24, wherein the ions comprise magnesium, manganese, zinc or silicon ions.

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FIGURE 1



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/01170

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 A61L H01J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 917 702 A (SCHEICHER HANS ET AL) 17 April 1990 (1990-04-17)  abstract column 1, line 48-50 - column 2, line 52-56 column 3, line 65-67 - column 4, line 6,7,35-68 column 16, line 3-9; claims 14-17 ---	1-3, 8-14,16, 17,22-25
Y	US 4 800 884 A (HEIDE JORGAN ET AL) 31 January 1989 (1989-01-31)  abstract column 2, line 47-52 - column 3, line 6-21 column 6, line 60-68 ---	1-6, 8-14, 16-20, 22-25
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 99/01170

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 4 718 905 A (FREEMAN JERRE M) 12 January 1988 (1988-01-12) abstract column 3, line 50-66 - column 4, line 13-21,42-50,63-68 column 5, line 1-19 - column 9, line 61-67 column 11, line 56-64; claim 5 ---	1,3-7, 16,18-21
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